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Radical Azidonation of Aldehydes

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Aliphatic and aromatic aldehydes can be converted to acyl azides by treatment with iodine azide at 0−25 °C. If the reaction is performed at reflux Curtius rearrangement occurs and carbamoyl azides are obtained in 70−97% yield from the aldehyde. The reaction was shown to have a radical mechanism.

The azido group is a highly useful functionality in organic synthesis due to its ready conversion to amino groups or due to its photochemical or cycloaddition reactions. A range of methods for introduction of the azido group into organic molecules are known; however, free radical substitution has not been one of them.[1,2]

Nevertheless, the azidyl radical is readily formed by oxidation of azide ion by a variety of oxidation agents, and is an electrophilic species that is related to halogen and pseudohalogen radicals.[3,4]

Iodine azide is, while well-known for its ability of ionic addition to olefins, in fact able to undergo bond homolysis and provide radicals. We have recently shown that radical substitution with azide can be carried out on benzyl ethers to give α-azido ethers in high yield, using iodine azide (Scheme 1).[5] Benzal acetals are similarly converted to β-azidobenzoates by this reagent.[6] From these results it can be envisaged that other hydrogen compounds with low bond dissociation energies can undergo substitution with azide. In this paper we report that aldehydes can be converted to acyl azides by treatment with IN_3 at room temperature. If the reaction is carried out at elevated temperature the acyl azide undergoes spontaneous Curtius rearrangement to form a carbamoyl azide that can be hydrolyzed to the amine. The transformation of aldehydes to acyl azides has previously been reported to be possible with $CrO_3/TMSN_3$[7] or $MnO_2/SiCl_4/NaN_3$,[8] which presumably work by oxidation of an azido alcohol or through in situ formation of an acid chloride. The present method is therefore conceptually different.

SCHEME 1. Azidonation of Benzyl Ethyl Ether
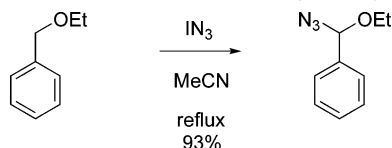
The C−H bond in aldehydes has a bond dissociation energy of 89 kcal/mol and should therefore be expected to be subject to facile attack. Nevertheless, the ease with which aromatic and aliphatic aldehydes were found to undergo reaction with IN_3 was remarkable. The results of the reaction of a series aldehydes with IN_3 in MeCN at 25 °C are given in Table 1. IN_3 is formed in situ by mixing ICl (2 equiv) and NaN_3 (3 equiv) in MeCN under conditions where it is not explosive.[9,10] In 2.5 h essentially quantitative conversion of aldehyde to acyl azide was seen by NMR (Table 1). By heating the acyl azide in toluene[11] it undergoes Curtius rearrangement to form in high yield the isocyanate.

However, since both acyl azides and isocyanates are reactive compounds that cannot be subjected to chromatography, it is convenient to carry out the reaction at reflux, which results in spontaneous Curtius rearrangement and formation of a carbamoyl azide by addition of azide to the isocyanate. Table 2 shows the results of reaction of aliphatic and aromatic aldehydes with IN_3 in MeCN at 83 °C with the yields given being the amount of carbamoyl azide isolated after chromatography.

Less polar solvents such as chloroform or CH_2Cl_2 are normally an advantage in radical reactions but the reaction gave lower yield in these solvents presumably because NaN_3 is poorly soluble. Interestingly, the reaction can be performed with BrN_3 formed in situ in MeCN from NBS and sodium azide. However, the yield is lower; from cyclohexyl carboxaldehyde a 42% yield of azidonation

(1) Recently Renaud's group has reported an elegant method for radical substitution with azide by adding alkyl radicals to ethanesulfonyl azide, see: (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496−6497. (b) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460−3462.

(2) Reactions that use $PhIO/TMSN_3$ to introduce azide α to amines and enol ethers may involve radicals, see: Magnus, P.; Lacour, J.; Weber, W. *J. Am. Chem. Soc.* **1993**, *115*, 9347−9348.

(3) Workentin, M. S.; Wagner, B. D.; Lusztyk, J.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1995**, *117*, 119−126.

(4) Fontana, F.; Minisci, F.; Yan, Y. M.; Zhao, L. *Tetrahedron Lett.* **1993**, *34*, 2517−2520.

(5) Viuf, C.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 623−625.

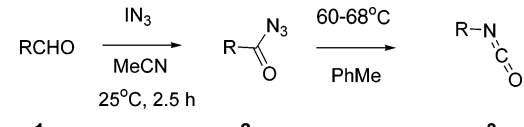(6) Baruah, M.; Bols, M. *Synlett.* **2002** 1111−1112.

(7) Lee, J. G.; Kwak, K. H. *Tetrahedron Lett.* **1992**, *33*, 3165−3166.

(8) Elmorsy, S. S. *Tetrahedron Lett.* **1995**, *36*, 1341−1342.

(9) Cambie, R. C.; Jurlina, J. L.; Ruthledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 315−27.
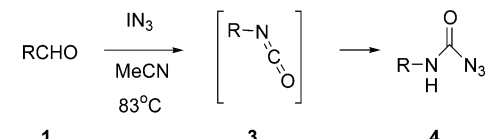
(10) Solid iodine azide is explosive and should never be allowed to form. We always generate the reagent in solution and destroy the reagent with thiosulfate wash before workup. When adhering to this we have not encountered any problems even on prolonged reflux.

(11) Allen, C. F. H.; Bell, A. *Organic Synthesis*; Wiley: New York; Collect. Vol. III, pp 846−847.

TABLE 1. Reaction of Aldehydes with Iodine Azide at Room Temperature and Subsequent Curtius Rearragement[a]

R	Nr	yield **2** (acyl azide) (%)	yield **3** (isocyanate) (%)
PhCH$_2$CH$_2$	**a**	82	97
CH$_3$(CH$_2$)$_8$	**b**	quant.	98
CH$_3$(CH$_2$)$_6$	**c**	86	99

[a] Yields determined by NMR.

TABLE 2. Reaction of Aldehydes with Iodine Azide (2 equiv of ICl and 3 equiv of NaN$_3$ in MeCN) at Reflux
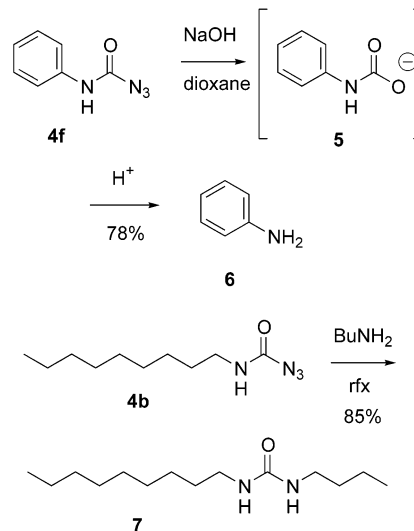

R	Nr	time (h)	yield[a] of **4**[12] (%)
CH$_3$(CH$_2$)$_6$	**c**	4	53[b]
		4	86
CH$_3$(CH$_2$)$_8$	**b**	4	84
PhCH$_2$CH$_2$	**a**	4	73
Me$_3$C	**d**	4	67
c-C$_6$H$_{12}$	**e**	4	89
Ph	**f**	4	97
p-MeOPh	**g**	4	70
p-MePh	**h**	4	96
o-MePh	**i**	4	74

[a] Yields are of carbamoyl azide after chromatography. [b] 1 equiv of ICl and 2.5 equiv of NaN$_3$.

product was obtained with this reagent. For comparison the reaction can be performed with NIS/NaN$_3$ but the reaction is much slower.

Carbamoyl azides[13] can be converted to amines, carbamates, or ureas and the reaction is therefore a valuable and simple route from aldehydes to amines or their derivatives. For example, hydrolysis of carbamoyl azide **4f** by cold NaOH gave instantaneously the carbamic acid **5** and after acidic workup the amine **6** (Scheme 2). Alternatively, reaction of carbamoyl azide **4b** with neat butylamine at reflux gave urea **7** in 85% yield.

To gain support for the hypothesis that the reaction followed a radical mechanism the reaction of phenylpropanal with IN$_3$ at 25 °C (Table 1) was performed in the presence of the radical trap **8** (0.5 equiv). No acyl azide was observed after 2.5 h, which was taken as support for a radical reaction mechanism. Furthermore, carrying out the IN$_3$ reaction of cyclohexyl carboxaldehyde in

(12) Most of these carbamoyl azides are known compounds described in the following papers: (a) Reddy, P. S.; Yadagiri, P.; Lumin, S.; Shin, D.-S.; Falck, J. R. *Synth. Commun.* **1988**, *18*, 545−551. (b) Affandi, H.; Bayquen, A. V.; Read, R. W. *Tetrahedron Lett.* **1994**, *35*, 2729−2732. (c) Rawal, V. H.; Zhong, H. M. *Tetrahedron Lett.* **1994**, *35*, 4947−4950. (d) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151−2157.

(13) Lieber, E.; Minnis, R. L. *Chem. Rev.* **1965**, *65*, 377−384.

SCHEME 2. Some Transformations of Carbamoyl Azides

SCHEME 3. Radical Trap 8 and a Proposed Mechanism of the Reaction
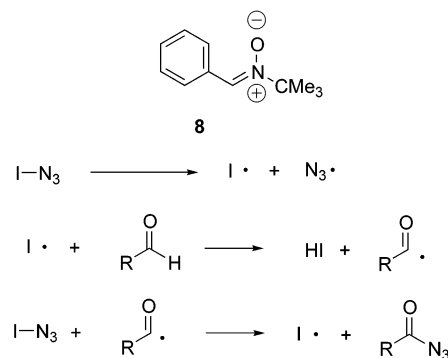
EtOH led to complete conversion of starting material and carbamoyl azide being the major product. No cyclohexyl carboxylic acid ethyl ester was observed, which shows that the acid iodide or acylonium ion cannot be intermediates in the reaction.

On the basis of these results the mechanism shown in Scheme 3 is proposed for the reaction. Iodine radicals are formed by homolysis of the weak iodine−azide bond, abstracting the aldehyde hydrogen atom. The resulting carbon-centered radical reacts with iodine azide to produce an acyl azide and an iodine radical. Overall the reaction produces HI as a byproduct.

This new reaction constitutes a facile direct route from aldehydes to amines, carbamates, or ureas containing one carbon less. In cases where this transformation is desired it constitutes a shorter route than the conventional Curtius rearrangement. It should be a valuable addition to the synthetic arsenal.

Experimental Section

Warning: Iodine azide is potentially explosive and definitely so in solid form. The reagent should be generated in solution and destroyed with thiosulfate wash before workup. When adhering to this we have not encountered any problems even on prolonged reflux. However, when solid NaN$_3$ and ICl are mixed an explosion occurs.

Azidonation at Room Temperature (25 °C). To a stirred slurry of 3 mmol of sodium azide (195 mg) in 3 mL of acetonitrile in an ice bath was added slowly 2 mmol of iodine monochloride in 3 mL of acetonitrile. The reaction mixture was stirred for an additional 5−10 min, and 1 mmol of the aldehyde was added. The reaction was allowed to reach room temperature and was stirred for 2.5 h. The red-brown slurry was poured into 5 mL of water, and the mixture was extracted with dichloromethane (10 mL). The organic extracts were combined and washed with 10 mL of 5% sodium thiosulfate leaving a colorless solution, which was dried over magnesium sulfate. Removal of the solvent under reduced pressure produced acyl azide.

Curtius Rearrangement. The acyl azide was dissolved in 5 mL of dry toluene. The solution of acyl azide in toluene was added dropwise to 15 mL of hot toluene and heated to 60−68 °C for 1 h or more. Afterward, the toluene was removed at reduced pressure and the product was analyzed by NMR.

Azidonation at Reflux (83 °C). To a stirred slurry of 3 mmol of sodium azide (195 mg) in 3 mL of acetonitrile in an ice bath was added slowly 2 mmol of iodine monochloride (325 mg) in 3 mL of acetonitrile over a period of 10−20 min. Then 1 mmol of the aldehyde was added and the reaction mixture was refluxed for 4 h, cooled, poured into 10 mL of water, and extracted with dichloromethane (10 mL). The organic extracts were washed with 5% sodium thiosulfate solution (10 mL) leaving a colorless organic solution, which was dried over magnesium sulfate, filtered, evaporated under reduced pressure, and finally subjected to flash chromatography in the indicated solvent mixture.

Supporting Information Available: Experimental and spectroscopic details for compounds **2a**−**c**, **3a**−**c**, **4a**−**i**, and **7**, procedures for the synthesis of **6** and **7**, general experimental descriptions, and ^{13}C NMR spectra of **4b**, **4d**, **4h**, and **4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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